The Molecular Biology of Cancer

Delaney Sullivan
dsull@stanford.edu
Undergraduate Student, Stanford University
April 11, 2015
Review

• Central Dogma of Molecular Biology
• Mendelian Genetics
• Types of mutations: silent, missense, nonsense, frameshift
Introduction to Cancer
What is Cancer?

Cancer is:

• Malignant *neoplasia*
• A non-communicable disease
• Responsible for 1 in 4 deaths in the U.S.
Cancer is an Ancient Malady

Edwin Smith Papyrus
• Earliest mention of cancer
  • Circa 1600 BCE
• “There is no treatment”
Origin of the Word “Cancer”

Karkinos
• *Hippocrates*, ca. 400 BCE
• Greek word for crab

Cancer
• *Celsus*, 28-50 BCE
• Roman word for crab

Onkos
• *Galen*, 130-200 CE
• Greek word for “large mass”
• Origin of the word “oncology”
Cancer Deaths on the Rise

Cancer Deaths on the Rise

Reasons?
- Increasing population
- Increase in life expectancy

Cancer Classification

• Carcinoma: Cancer derived from epithelial tissue
  • Adenocarcinoma: Cancer of epithelial “glandular” tissue
  • Squamous cell carcinoma: Cancer of flat, surface-covering cells

• Sarcoma: Cancer derived from cells that form connective tissue

• Myeloma: Cancer derived from plasma cells of bone marrow

• Leukemia: Cancer of blood-forming cells

• Lymphoma: Cancer of the lymphatic system

• Blastoma: Cancer that arises from undifferentiated embryonic cells
Cancer Classification

• Carcinoma: Cancer derived from epithelial tissue
  • Adenocarcinoma: Cancer of epithelial “glandular” tissue
  • Squamous cell carcinoma: Cancer of flat, surface-covering cells

• Sarcoma: Cancer derived from cells that form connective tissue

• Myeloma: Cancer derived from plasma cells of bone marrow

• Leukemia: Cancer of blood-forming cells

• Lymphoma: Cancer of the lymphatic system

• Blastoma: Cancer that arises from undifferentiated embryonic cells

• Other types (e.g. teratomas)
Teratoma
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. bacteria)
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. bacteria)
• Hereditary factors
• Random chance

H. pylori
What Causes Cancer?

Cancer is caused by many different things:

- Environmental factors (e.g. viruses)
- Hereditary factors
- Random chance
What Causes Cancer?

Cancer is caused by many different things:
• Environmental factors (e.g. viruses)
• Hereditary factors
• Random chance

HPV-18
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. viruses)
• Hereditary factors
• Random chance

Epstein-Barr virus
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. radiation)
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:
• Environmental factors (e.g. radiation)
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. immune system)
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. carcinogens)
• Hereditary factors
• Random chance
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors (e.g. carcinogens)
• Hereditary factors
• Random chance

Most carcinogens are mutagens and can be identified by the Ames test
What Causes Cancer?

Cancer is caused by many different things:

• Environmental factors
• Hereditary factors (e.g. BRCA1 and BRCA2)
• Random chance
What Causes Cancer?

Cancer is caused by many different things:
• Environmental factors
• Hereditary factors
• Random chance (e.g. Errors in DNA replication / repair)
What Causes Cancer?

Cancer is caused by many different things:
• Environmental factors
• Hereditary factors
• Random chance

Cancer is the result of mutations:
• Germline mutations
• Somatic mutations
Hallmarks of Cancer
Recap

- Cancer is a widespread non-communicable disease characterized by malignant neoplasia
- Cancer is an ancient illness
- Increasing number of deaths caused by cancer is due to an increase in population size and life expectancy
- Cancer has many causes but ultimately is the result of mutations
- Cancer evolves via natural selection to acquire certain “hallmarks” (survival advantages).
Oncogenes and Tumor Suppressor Genes
Oncogenes vs. Tumor Suppressor Genes

**Oncogenes**: Promote tumorigenesis

- The activated form of a proto-oncogene
  - *Proto-oncogenes* are normal genes that can become oncogenic when mutated or overexpressed
- Mutations typically dominant

**Tumor suppressor genes**: Suppress tumorigenesis

- Loss of function can lead to cancer
- Mutations typically recessive (*loss-of-heterozygosity*)
Oncogenes vs. Tumor Suppressor Genes

**Oncogenes**: Promote tumorigenesis

- The activated form of a proto-oncogene
  - **Proto-oncogenes** are normal genes that can become oncogenic when mutated or overexpressed
- Mutations typically dominant

**Tumor suppressor genes**: Suppress tumorigenesis

- Loss of function can lead to cancer
- Mutations typically recessive (**loss-of-heterozygosity**)
Oncogenes vs. Tumor Suppressor Genes

*Question:* You notice that gene “A” is frequently mutated in cancers. 90% of the mutations are either nonsense or frameshift mutations while 10% of the mutations are missense mutations.

Is gene “A” likely to be a proto-oncogene or a tumor suppressor gene?
Oncogenes vs. Tumor Suppressor Genes

**Question:** You notice that gene “A” is frequently mutated in cancers. 90% of the mutations are either nonsense or frameshift mutations while 10% of the mutations are missense mutations.

Is gene “A” likely to be a proto-oncogene or a tumor suppressor gene?

**Answer:** A tumor suppressor gene
Oncogenes vs. Tumor Suppressor Genes

Thought Questions:

What is the normal function of proteins encoded by proto-oncogenes?

What is the normal function of proteins encoded by tumor suppressor genes?
History of Oncogenes: Rous Sarcoma Virus

• **Peyton Rous** injected a tumor from one chicken into another
  • Discovered that cancer could be transmitted from chicken to chicken!

• Possible interpretations of Rous’s experiment?
History of Oncogenes: Rous Sarcoma Virus

- **Peyton Rous** injected a tumor from one chicken into another
  - Discovered that cancer could be transmitted from chicken to chicken!
- Possible interpretations of Rous’s experiment?
  - Cancer in the second chicken caused by cancer cells from the original chicken
  - Cancer in the second chicken caused by something else from original chicken
History of Oncogenes: Rous Sarcoma Virus

• **Peyton Rous** injected a tumor from one chicken into another
  • Discovered that cancer could be transmitted from chicken to chicken!

• Possible interpretations of Rous’s experiment?
  • Cancer in the second chicken caused by cancer cells from the original chicken
  • Cancer in the second chicken caused by something else from original chicken

• Peyton Rous passed the tumor cells through a set of very fine filters and injected the filtrate (without the cells) into another chicken
  • That chicken still developed cancer!
  • Seemed to contradict the “carcinogen theory” of cancer
History of Oncogenes: Rous Sarcoma Virus

• How did Peyton Rous’s chickens develop cancer?
  • From a virus, now called Rous Sarcoma Virus (RSV).
• Thus emerged the virus theory of cancer.
“What can be the nature of the generality of neoplastic changes, the reason for their persistence, their irreversibility, and for the discontinuous, steplike alterations that they frequently undergo? A favorite explanation has been that oncogenes cause alterations in the genes of the cells of the body, somatic mutations as these are termed. But numerous facts, when taken together, decisively exclude this supposition.”

- Peyton Rous, Nobel Lecture, 1966
History of Oncogenes: Retroviral Oncogenes

• RSV’s genome contained only 4 genes.
  • RSV’s cancer-causing ability was pinpointed in a gene called src.
• Question: Where did src come from?
• **Michael Bishop** and **Harold Varmus**’s experiment:
History of Oncogenes: Retroviral Oncogenes

• RSV’s genome contained only 4 genes.
  • RSV’s cancer-causing ability was pinpointed in a gene called src.
• Question: Where did src come from?
• Michael Bishop and Harold Varmus’s experiment:

\[\text{src cDNA hybridizes with chicken DNA! Therefore src is present in chicken DNA!}\]
History of Oncogenes: Retroviral Oncogenes

• RSV’s genome contained only 4 genes.
  • RSV’s cancer-causing ability was pinpointed in a gene called src.
• Question: Where did src come from?
• Michael Bishop and Harold Varmus’s experiment:

src cDNA hybridizes with chicken DNA! Therefore src is present in chicken DNA!

Which came first? The chicken src or the viral src?
History of Oncogenes: Retroviral Oncogenes

- RSV’s genome contained only 4 genes.
  - RSV’s cancer-causing ability was pinpointed in a gene called src.
- Question: Where did src come from?
- Michael Bishop and Harold Varmus’s experiment:

\[
\text{src cDNA hybridizes with chicken DNA!}
\text{Therefore src is present in chicken DNA!}
\]

The src cDNA probe reacted to quail, duck, human, and mouse DNA but less well.
History of Oncogenes: Retroviral Oncogenes

• Conclusion: Virus stole the src gene from chicken!
  • The viral src contains a mutation that renders it oncogenic.
  • Chicken src = proto-oncogene (a normal gene that can become oncogenic)

Mike Bishop (left)
Harold Varmus (right)

Nobel Prize recipients, 1989
History of Oncogenes: Retroviral Oncogenes

- Additional note: Not all cancer-causing viruses possess oncogenes
  - Some can induce cancer via *insertional mutagenesis*. 
History of Tumor Suppressor Genes

• Henry Harris discovered that fusing a cancer cell with a normal one can result a normal fusion cell.
  • Could be due to a gene that suppresses the neoplastic phenotype.

• Alfred Knudson’s statistical analysis revealed that inherited retinoblastoma resulted in earlier onset, bilateral, multiple tumors whereas sporadic retinoblastoma resulted in late onset, unilateral, single tumors. **Two-hit hypothesis**:
  • Inherited retinoblastoma: First “hit” was inherited in the DNA. Just one sporadic mutation would then lead to cancer.
  • Sporadic retinoblastoma: Two sporadic mutations necessary to cause cancer.
Oncogenes vs. Tumor Suppresser Genes

**Oncogenes**: Promote tumorigenesis

- The activated form of a proto-oncogene
  - **Proto-oncogenes** are normal genes that can become oncogenic when mutated or overexpressed
- Mutations typically dominant

**Tumor suppressor genes**: Suppress tumorigenesis

- Loss of function can lead to cancer
- Mutations typically recessive (*loss-of-heterozygosity*)
The gene: p53

p53:
• Most frequently mutated gene in human cancer.
• Is it a proto-oncogene or a tumor suppressor gene?
The gene: p53

p53 Knockout Mice Are More Susceptible to Tumors

Harvey et al., 1993
The gene: \textit{p53}

\textit{p53 Knockout Mice Are More Susceptible to Tumors}

Harvey et al., 1993

What is the deal with the +/- mice?

Harvey et al., 1993
The gene: p53

p53 Knockout Mice Are More Susceptible to Tumors

Harvey et al., 1993
The Tumor Suppressor: p53

p53:
• “The Guardian of the Genome”
• Wild-type p53 functions as a transcriptional activator that promotes expression of genes involved in cell cycle arrest, DNA repair, and apoptosis in response to DNA damage or cellular stress.
• Functions as a tetramer
• Many mutations are dominant negative
Recap

• Cancer is a widespread non-communicable disease characterized by malignant neoplasia
• Cancer is an ancient illness
• Increasing number of deaths caused by cancer is due to an increase in population size and life expectancy
• Cancer has many causes but ultimately is the result of mutations in proto-oncogenes and tumor suppressor genes
• Cancer evolves via natural selection to acquire certain “hallmarks” (survival advantages).
Tumorigenesis
All cells arise from pre-existing cells

Cell theory:
- All cells arise from pre-existing cells
  - omnis cellula e cellula

Rudolf Virchow
Does cancer arise from a single cell?

• Question: Are tumors **monoclonal** or **polyclonal**?
Does cancer arise from a single cell?

• Question: Are tumors **monoclonal** or **polyclonal**?

• Experiment: X-inactivation
  • In human females, one X chromosome is inactivated during gastrulation.
    • The choice of which X is inactivated is **random**.
  • Say we have a female cancer patient who’s heterozygous for an X-linked character named “A”
    • Her genotype would be: $X^AX^a$
  • Result: All cells from her tumor express the same allele for the “A” character
    • e.g. all cells are $X^aX^a$
  • Conclusion: Tumors are **monoclonal**
Does cancer arise from a single cell?

• Question: Are tumors **monoclonal** or **polyclonal**?

• Experiment: B cell antibodies
  • B cells are white blood cells that produce antibodies.
  • A healthy immune system has millions of B cell subpopulations, each expressing a unique antibody.
  • In **myeloma** (cancer of mature B cells), all the myeloma cells express the same antibody.

• Conclusion: Tumors are **monoclonal**
Cancer is a multistep process

- Tumorigenesis is a multistep process
  - A single mutation is not enough to cause cancer
Cancer is a multistep process

• Tumorigenesis is a multistep process
  • A single mutation is not enough to cause cancer

Genomic instability:
Accumulation of:
• driver mutations
• passenger mutations
Recap

• Cancer is a widespread non-communicable disease characterized by malignant neoplasia
• Cancer is an ancient illness
• Increasing number of deaths caused by cancer is due to an increase in population size and life expectancy
• Cancer has many causes but ultimately is the result of mutations in proto-oncogenes and tumor suppressor genes
• **Cancer is monoclonal and is a multistep process**
• Cancer evolves via natural selection to acquire certain “hallmarks” (survival advantages).
Therapy
Classic Cancer Therapy

• Surgery
• Radiation
• Chemotherapy
Classic Cancer Therapy

• Surgery
• Radiation
• Chemotherapy

Sidney Farber
• Father of chemotherapy
• Discovered the use of antifolates in cancer treatment
Targeted therapy

Oncogene addiction

• Inactivation of a single oncogene can induce tumor regression.

Two types of drugs:

• Biologics (e.g. antibodies)
• Small molecules
Targeted therapy

Oncogene addiction
• Inactivation of a single oncogene can induce tumor regression.

Two types of drugs:
• Biologics (e.g. antibodies)
• Small molecules

Some targets are not druggable
Epidermal Growth Factor Receptors

(a) Structure of the epidermal growth factor (EGF) receptor

(b) Activation of the EGF receptor

Cellular Response
Epidermal Growth Factor Receptors

EGFRs are druggable proto-oncogenes.

Cellular Response
Herceptin

• HER2 receptor is overexpressed in certain breast cancers.
• Genentech developed **Herceptin**, an antibody against HER2 receptors.
  • Herceptin binds to HER2 receptor and inhibits its activity.
• Adding Herceptin to chemotherapy improves overall survival by 37%.
**Gleevec** is a small molecule used in treatment of **CML**:

- CML is caused by a translocation.
- The translocation results in a novel toxic fusion protein (**BCR/ABL**) that is a constitutively active EGFR.
- Gleevec inhibits BCR/ABL.
Gleevec

**Brian Druker**, developer of Gleevec (imatinib) “estimated overall survival of patients who received imatinib as initial therapy was 89% at 60 months” (Druker et al., NEJM, 2006)
Immunotherapy

- **CD47** expression on cell surface allows cells to avoid phagocytosis.
  - “Don’t eat me” signal to *macrophages*.
- Cancer cells oftentimes express high levels of CD47.
- Blocking CD47 with an antibody turns off “don’t eat me signal”.
  - Cancer cells get eaten up by macrophages.
  - Other immune cells may get activated to launch an attack against the cancer.
Understanding the molecular underpinnings of cancer will lead to cures
Cancer prevention:
Minimizing exposure to environmental carcinogens (e.g. asbestos and tobacco) reduces the risk of cancer
Cancer Relapse

• Why do cancers recur after treatment?
  • Not all cancer cells were eliminated from the treatment
    • Extremely difficult to eliminate all traces of cancer, especially after metastasis
  • Natural selection
    • Cancer cells that can resist the treatment survive and proliferate
Cancer is a widespread non-communicable disease characterized by malignant neoplasia.

Cancer is an ancient illness.

Increasing number of deaths caused by cancer is due to an increase in population size and life expectancy.

Cancer has many causes but ultimately is the result of mutations in proto-oncogenes and tumor suppressor genes.

Cancer is monoclonal and is a multistep process.

Cancer evolves via natural selection to acquire certain “hallmarks” (survival advantages). Evolution explains why cancers relapse.

Targeted therapy and immunotherapy are promising.
Laboratory Animals in Research
“If Peyton Rous had been denied his chickens, our field would have no past; if all of us are now denied mice and other animals, it will have little future.” – Harold Varmus
Acknowledgements

• Stanford University
• SPLASH
• All of you
Recommended Reading

The Emperor of All Maladies
Siddhartha Mukherjee

The Biology of Cancer
Second Edition
Robert A. Weinberg
Thank you